

CHAPTER 5

DISCUSSION AND CONCLUSION

The mean quetiapine plasma concentration-time profiles after an oral administration of a single oral dose of the test and reference formulations were comparable and exhibited closely similar pattern. The results showed that the mean and SD of the pharmacokinetic parameters of the two formulations were similar, indicating that the pharmacokinetics of quetiapine in the two formulations are similar. After single oral administration, the drug was rapidly absorbed and reached C_{max} at 1.08 and 1.10 h for the test and reference formulations, respectively. Mean peak of quetiapine levels of the test and reference formulations were 886.60 and 811.34 ng/ml, respectively. Plasma quetiapine level then declined, with the mean $T_{1/2}$ of 5.26 and 5.53 h for Quantia 200[®] and Seroquel[®], respectively. The pharmacokinetic parameters in these healthy Thai volunteers were similar to previously studies which also showed that quetiapine was rapidly absorption with T_{max} of 0.5-2 h (Davis *et al.*, 1999; Thyrum *et al.*, 2000; Wong *et al.*, 2001; Jaskiw *et al.*, 2004; Li *et al.*, 2004; Li *et al.*, 2005; Grimm *et al.*, 2005).

Previous studies have reported that the C_{max} and AUC of quetiapine after receiving a single dose of 25 mg in healthy subjects were 53-79 ng/ml and 248-366 ng.h/ml, respectively. When studied in multiple doses of 150, 250 and 300 mg, the C_{max} at steady-state were 437, 1,048 and 1,042 ng/ml, the AUC was 1,980, 3,642 and 4,650 ng.h/ml, respectively (Davis *et al.*, 1999; Wong *et al.*, 2001; Grimm *et al.*, 2005). Quetiapine does exhibit linear pharmacokinetics (Jaskiw *et al.*, 2004; Goren and Levin, 1998). In this study, the mean \pm SD of C_{max} of Quantia 200[®] and Seroquel[®] were 886.60 \pm 356.50 and 811.34 \pm 323.37 ng/ml, respectively. AUC_{0-48} were 3,754.41 \pm 1,453.00 and 3,520.00 \pm 1,229.61, $AUC_{0-\infty}$ were 4,015.35 \pm 1,528.25 and 3,769.45 \pm 1,296.69 ng.h/ml for Quantia 200[®] and Seroquel[®], respectively. The minimum and maximum of C_{max} of quetiapine were 287.31 and 1,806.53 ng/ml, respectively, which demonstrated large individual variation. The high variation of

C_{\max} depend on T_{\max} . Changes in the rate of drug absorption will result in changes in both C_{\max} and T_{\max} . When the rate of absorption is decreased, the T_{\max} is slower and C_{\max} will be lower. If the rate of absorption is increased, the T_{\max} is faster and C_{\max} will be higher. In this study, T_{\max} varied among individuals between 0.33-4 h, so C_{\max} was highly varied in individual subjects.

The $T_{1/2}$ of Quantia 200[®] (5.26 h) was similar to Seroquel[®] (5.53 h). $T_{1/2}$ of both formulations were markedly varied among individuals, between 1-11 h. This range of $T_{1/2}$ is similar to that of Li *et al.* (2004) who reports that $T_{1/2}$ can be varied between 5-10 h. The longer $T_{1/2}$ and significantly deviates from the common range may be resulted from the lower activity of CYP3A4. Li *et al.* (2004) reported that genetic polymorphism of *CYP* is the main factor for individual difference of metabolism for quetiapine and its metabolites. The activity of CYP3A4 is considered to be the major metabolizing enzyme for quetiapine (DeVane and Nemeroff, 2001).

In healthy subjects, the CL/f of quetiapine appears to be varied from 83-113 L/h, the CL/f of quetiapine is a characteristic of drugs with high hepatic extraction ratio and extensive first-pass elimination. Gastrointestinal CYP3A4 metabolism of quetiapine has not been reported (DeVane and Nemeroff, 2001). The CL/f of quetiapine given as a single dose (25 mg) is 86-105 L/h (Thyrum *et al.*, 2000), whereas in multiple dose with 150 mg of the drug t.i.d., the mean CL/f is 101 L/h (Davis *et al.*, 1999), when treated with quetiapine 250 mg t.i.d., the mean CL/f is 80.3 L/h (Wong *et al.*, 2001). In this study, the mean of CL/f of quetiapine after a single oral dose of 200 mg of both Quantia 200[®] and Seroquel[®] were 58.86 and 60.30 L/h. Clearance is often related to many factors such as body weight, renal excretion or hepatic metabolism (Thomson, 2004). In this study, clearance is much less than the above report, this might be related to lower body weight and less fat content of the subjects.

As quetiapine is highly lipophilic, therefore it is widely distributed throughout the body with an apparent volume of distribution (V_z/f) of 10 ± 4 L/kg (Goren and Levin, 1998). In a single dose study of quetiapine, the V_z/f is 455-593 L (Thyrum *et al.*, 2000). In multiple doses of 200 mg and 150 mg of quetiapine, the V_z/f are 672 and 671 L, respectively (Li *et al.*, 2004; Davis *et al.*, 1999). In the present

study V_z/f after a single dose of 200 mg of quetiapine were 384.62 and 437.59 L for Quantia 200[®] and Seroquel[®], respectively, which were much less than those of the above reports. This might be related to the less fat content in Thai than Caucasian subjects.

A high inter-individual variation in plasma concentration was also observed by Davis *et al.* (1999) and Li *et al.* (2004) who reported that % CV of C_{max} and AUC were about 40% and more than 50%, respectively. In the present study, the plasma concentrations of quetiapine were varied and the % CV of C_{max} and AUC were similar to the above reports. The high variation of pharmacokinetic parameters of individual is mainly due to difference in metabolism and uniform of products.

In addition, many subjects showed double peaks of quetiapine after receiving Quantia 200[®] and Seroquel[®]. The rationale for the double peaks phenomenon has been attributed to variability in stomach emptying, variable intestinal motility, presence of food, enterohepatic recycling or uniform of the products (Shargel *et al.*, 2005). In this study, double peaks were proposed to be due to difference in the enterohepatic circulation. Granero and Amidon (2007) also suggested that enterohepatic circulation is a likely explanation for multiple peaks in ketoprofen plasma concentrations. In theory, drug or its metabolites which are excreted into bile are usually glucuronide conjugated. After that it is excreted into the duodenum via the common bile duct. Subsequently the drug or its metabolites may be excreted into the feces or the drug may be reabsorbed and become systemically available, so the drug that undergo enterohepatic circulation shows secondary peak in the plasma drug-concentration curve (Shargel *et al.*, 2005)

The results from the ANOVA study showed that formulation, sequence and period had no significant effect on C_{max} , AUC_{0-48} and $AUC_{0-\infty}$ at the significant level of 0.05. The results showed that all the pharmacokinetic parameters of both products were similar. The 90% CI of C_{max} , AUC_{0-48} and $AUC_{0-\infty}$ for Quantia 200[®]/Seroquel[®] were 98.21-124.37%, 94.43-117.03% and 94.77-116.61%, respectively (Table 22). These values were within the acceptable range of the Thai FDA criteria, i.e. 80-125%.

The power of the tests obtained from the present study for pharmacokinetic parameters C_{\max} , AUC_{0-48} and $AUC_{0-\infty}$ was found to be 92.1, 96.9 and 97.4%, respectively. This shows that the sample size in this study was adequate based on the data for C_{\max} , AUC_{0-48} and $AUC_{0-\infty}$, thus the power of the test was considered adequate in this study.

The adverse events associated with quetiapine were mild to moderate. In this study, somnolence was the dominant adverse event for both formulations. All subjects were somnolence (100%) within 1 h after taking the drug which is similar to the report of Thyrum *et al* (2000) and Grimm *et al.* (2005). Other adverse events were orthostatic hypotension and agitation. These manifestations were minor adverse events described for quetiapine. Antagonism at H_1 and adrenergic α_1 -receptors, may explain the somnolence and orthostatic hypotension, respectively. (Jaskiw *et al.*, 2004). No serious adverse events were observed during quetiapine treatment and no subject withdrew because of adverse events.

In conclusion, the bioequivalence study in Thai male volunteers, 200 mg of quetiapine tablet were assessed. C_{\max} , AUC_{0-48} and $AUC_{0-\infty}$ obviously revealed no significant difference between Quantia 200[®] and Seroquel[®]. The 90% CI of the ratios of C_{\max} (98.21-124.37%), AUC_{0-48} (94.43-117.03%) and $AUC_{0-\infty}$ (94.77-116.61%) for the test and reference products were within the 80-125%, which is the acceptable range of the Thai FDA guidelines. Therefore, it was concluded that the two quetiapine formulations are bioequivalent in both the rates and extents of absorption.